Placebo response in asthma: A robust and objective phenomenon

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Background: Placebos are hypothesized to exert positive effects on medical conditions by enhancing patient expectancies. Recent reviews suggest that placebo benefits are restricted to subjective responses, like pain, but might be ineffective for objective physiologic outcomes. Nevertheless, mind-body links and placebo responsivity in asthma are widely believed to exist.
Objective: We carried out a randomized, double-blind investigation to (1) determine whether placebo can suppress airway hyperreactivity in asthmatic subjects, (2) quantify the placebo effect, (3) identify predictors of the placebo response, and (4) determine whether physician interventions modify the placebo response.
Methods: In a double-blind, crossover design investigation, 55 subjects with mild intermittent and persistent asthma with stable airway hyperreactivity were randomized to placebo or salmeterol before serial methacholine challenges. Subjects were additionally randomized to physician interactions that communicated either positive or neutral expectancies regarding drug effect.
Results: Placebo bronchodilator administration significantly reduced bronchial hyperreactivity compared with baseline (the calculated concentration of methacholine required to induce a 20% decrease in FEV_1 nearly doubled); 18% of subjects were placebo responders by using conservative definitions. Experimental manipulation of physician behavior altered perceptions of the physician but not the magnitude or frequency of the placebo response.
Conclusions: Objective placebo effects exist in asthma. These responses are of significant magnitude and likely to be meaningful clinically. The placebo response was not modulated by alterations in physician behavior in this study.
Clinical implications: The placebo response in patients with asthma is important in understanding the limitations of clinical research studies and in maximizing safe and effective therapies. This article confirms the existence of a strong placebo response in an objective and clinically relevant measure of disease activity. (J Allergy Clin Immunol 2007;119:1375-81.)

Key words: *Asthma, placebo, mind-body, psychology, bronchial hyperresponsiveness, central nervous system*

Recently, there has been a reawakening of interest in the placebo response. The term *placebo*, Latin for ''I shall please,'' was coined in the early 19 th century to describe a medicine ''adapted more to please than benefit the patient.''[1] Current ethical standards forbid the deceptive use of placebo to treat patients, but placebos are now often mandatory as controls in clinical studies of new therapeutics. In both cases, the placebos are assumed to have no significant effect on health. However, across a large number of clinical trials, benefit is often demonstrated in the placebo arm, raising the question of whether placebos can have psychologic, physiologic, and/or health effects.

A definitive health benefit from placebos cannot be inferred from clinical trials when the natural variation in the disease outcome is not measured because of the inability to differentiate between placebo effects and normal variability in disease status. A meta-analysis of placebo responses in clinical studies that did contain a natural history arm found that placebo administration induced beneficial changes in subjectively assessed outcomes, such as pain and depression, but not in objectively defined medical outcomes.[2] Although this report has been widely debated, it clearly questions the notion that placebos can affect peripheral physiologic processes or disease manifestations.

A primary aim of the current study was to determine whether there is a placebo response in objective measures of lung function in the context of asthma and, if so, to estimate the magnitude of that effect relative to natural variation in lung function and response to active drug. Asthma is a good disease model in which to study the placebo effect because disease-relevant objective end points can be assessed, such as air flow and bronchial hyperresponsiveness. Also, there is a long history of belief that psychologic factors play a role in the course of asthma, which is supported by recent research.[3-6] In the current study we compared the protective effect of the

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Abbreviations used
BMI: Body mass index
PC_{20}: Calculated concentration of methacholine required to induce a 20% decrease in FEV_1
PD_{20}: Dose level of methacholine during which a 20% decrease in FEV_1 was noted

long-acting bronchodilator salmeterol with placebo (the identical dry powder inhaler emptied of medication) when administered before a methacholine challenge.

A second aim was to determine the cognitive and affective mediators of the placebo effect. We hypothesized that treatment outcome expectancies—beliefs about a treatment's efficacy—would mediate placebo effects on airway hyperresponsiveness.[7-9] Expectancies regarding treatment outcome and disease course have predicted a variety of health outcomes, although most often in the setting of subjectively assessed measures.[10-15]

A third aim of the study was to determine whether the placebo response can be enhanced by induction of positive expectancies by a physician before placebo administration. Physician behavior was scripted to enhance (or not) positive treatment outcome expectancies and emotional care, the provision of support, empathy, reassurance, and warmth.[16] A review of studies that manipulated one or both of these dimensions of physician behavior demonstrates that positive health outcomes can result from these behavior patterns.[16]

METHODS

Participants

Subjects were recruited at the National Jewish Medical and Research Center and the University of Iowa. Eligible subjects were men and women, aged 18 to 55 years, with mild intermittent or persistent asthma[17] and a baseline FEV_1 of 80% of predicted value or greater. Major exclusion criteria included pregnancy or breast-feeding, serious systemic illness, recent respiratory tract infection, use of inhaled corticosteroids or other controller medications within 4 weeks, and smoking (>5 pack-year lifetime history). All subjects provided written informed consent before screening that did not reveal that the central purpose of the study was to explore the placebo response; this deception was revealed at a debriefing at the end of the protocol, when subjects were reconsented and given the opportunity to withdraw from the study. This study was reviewed and approved by the Institutional Review Boards of the University of Iowa; the University of California, San Francisco; the University of Missouri, Kansas City; and the University of Pennsylvania.

Procedures

Trial design. The study used a randomized, placebo-controlled trial design that included a crossover and required 6 visits (Fig 1). The first 3 visits (approximately 1 week apart) were used for screening and to establish the subjects' baseline characteristics, including the degree of airway hyperresponsiveness in the untreated state and after pretreatment with salmeterol (50 μg, Serevent Diskus, GSK, Research Triangle Park, NC). At visit 1, they were required to have a calculated concentration of methacholine required to induce a 20% decrease in FEV_1 (methacholine PC_{20}) of 4.0 mg/mL or less, with a second challenge (visit 2, a week later) positive within 1 dose level of the initial value. At visit 3, they needed to demonstrate significant protection (at least 1 dose level of improvement in PC_{20}) after inhalation of salmeterol (50 μg, Serevent Diskus, administered in a single-blind manner). The second phase of the study (visits 4 and 5) included a double-blind randomized intervention before methacholine challenge: administration of either placebo (Serevent Diskus from which the blister tape containing salmeterol was removed) or salmeterol, with a crossover to the alternate treatment arm. For these visits, the subjects were also randomized to receive *enhanced* or *efficient* interactions with a physician investigator (described below) before the administration of the active/sham inhaler: thus 4 groups were constituted by treatment order (placebo/salmeterol and salmeterol/placebo) and physician interaction (enhanced vs efficient). Finally, visit 6 consisted of a debriefing interview, at which time research subjects were informed that the central purpose of the study was to study placebo rather than treatment response and were provided the opportunity to withdraw their data from analysis with no penalty (not requested by any participant). Psychologic assessment included multiple questionnaires throughout the study (see below) that were administered with the goal of predicting placebo responsiveness. Other factors used in this analysis included sex, age, weight, and body mass index (BMI).

Pulmonary function measurement. Methacholine challenge testing was carried out according to standard procedures[18] to measure airway hyperresponsiveness, with serial doubling doses (diluent, 0.16, 0.31, 0.63, 1.25, 2.5, 5, 10, and 25 mg/mL) of methacholine aerosols with a calibrated dosimeter. The testing technician was blind to conditions. Each subject's screening methacholine PC_{20} (an average of the PC_{20} measured at visits 1 and 2) served as the baseline for comparison with subsequent challenges. The methacholine challenges during visits 4 and 5 were carried out 1 hour after the subject's use of the active/sham inhaler.

Physician encounters. On the basis of the literature, we proposed that a positive treatment outcome expectation communicated by the physician at the time of bronchodilator administration would increase positive expectancies regarding the treatment efficacy and thus enhance (or in the case of placebo induce) its physiologic effects. The *enhanced* physician encounter was designed to emphasize positive expectations, as well as the authority and supportiveness of the physician, whereas the *efficient* encounters minimized these factors, although they did not convey negative expectations. Enhanced and efficient physician investigators were selected by each site's principal investigator; all had expertise in asthma and possessed an interpersonal style matching either the enhanced or efficient style. Physicians who conducted the enhanced encounters were trained to transmit a positive expectation about the bronchodilator efficacy (for both of the crossover conditions) in reducing methacholine-induced symptoms by using specific scripted sentences (eg, ''You shouldn't have any symptoms''). Enhanced physician encounters also promoted authority (physicians wore a white coat and tie, were introduced as asthma experts, and were trained to speak with authority and conviction) in a supportive environment (encounters were longer, approximately 10 minutes, and included empathetic and respectful behavior, such as shaking hands with the subject). Physicians assigned to the efficient encounters were trained to convey an equivocal expectation about the bronchodilator efficacy (''It might work, and then again it might not'') and to minimize authority (no white coat or tie; introduction as a junior member of the team) and supportiveness (eg, encounters were about 2 minutes, and physicians displayed more efficient and brusque, although not negative, behaviors, such as inconsistent eye contact). The physician encounters took place just before administration of the salmeterol or placebo during visits 4 and 5. For the enhanced encounters, there was an additional brief interaction between the physician and patient immediately before the methacholine challenge. Training took place on site by an expert in

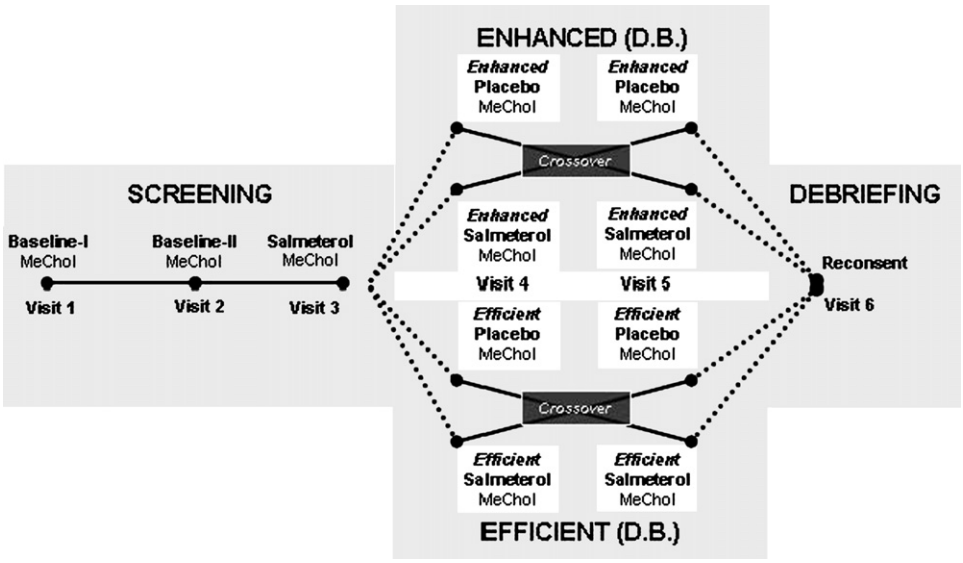

FIG 1. Trial design. As described in the Methods section, eligibility was determined at 3 screening visits, after which subjects were randomized to enhanced or efficient physician interactions and to order of premethacholine challenge treatment (with a crossover between salmeterol and placebo), followed by a final visit for reconsenting the subjects. *D.B.*, Double blind; *MeChol*, methacholine challenge.

the promotion of physician behaviors that motivate patient behavioral change. Each physician was trained in an individual half-day session. During the trial, encounters were audio taped and reviewed by the trainer for maintenance and reinforcement of appropriate behaviors.

Psychologic assessment. Psychologic instruments were included in an effort to predict the placebo response and to serve as a manipulation check for the physician encounters. Assessment took place at the screening visits, as well as before and after the physician encounters, and focused on mood state (including depression, hostility, and anxiety), as well as appraisals of current and future health, treatment, and the physician. The following instruments were used: the Positive Affect Negative Affect Schedule, the Beck Depression Inventory, the Spielberger State Anxiety Scale, the Affect Balance Scale, the Cooke-Medley Hostility Scale, the Life Orientation Test, the Marlowe-Crown Social Desirability Test, and the Health Locus of Control scale. The Asthma Stroop Task[19] was administered as a measure of asthma-specific cognitive interference and attentional biases. All standardized questionnaires used have good psychometric properties.

Statistical analyses

Between-group comparisons (enhanced vs efficient condition effects; placebo responders vs nonresponders) with PC_{20} and psychologic variables as dependent variables were conducted with *t* tests and confirmed with nonparametric Wilcoxon rank sum tests. Paired *t* tests were used for within-subject comparisons (eg, PC_{20} at the placebo vs screening visits). Mixed-model ANOVAs were also performed with PC_{20} values as the dependent variable, including between-subjects factors (enhanced vs efficient condition), within-subject factors (placebo visit vs salmeterol visit), and their interaction, as well as covariates.

RESULTS

Participants

Fifty-five subjects completed the study at 2 sites. Five subjects dropped out after the second screening visit; none were disqualified because of unstable airway hyperresponsiveness. The mean age of participants was 29.7 years (SD, 11.3); women comprised 56.4% of the population, and 91% of the sample was white. Mean BMI was 30.2 (SD, 6.5). There were no significant differences between those assigned to the enhanced and the efficient physician conditions in any demographic, psychologic, or medical variable assessed during the 3 screening visits, including baseline spirometry.

Existence of a placebo response

The first question to be addressed was whether a placebo response exists in airway hyperreactivity. We found that PC_{20} was significantly greater after administration of placebo than at baseline (the average of the untreated PC_{20} at visits 1 and 2; $P = .001$, Fig 2). We found no effect of treatment order (ie, no difference in degree of placebo response whether placebo was administered at visit 4 or visit 5). The response to salmeterol was significantly greater than that to placebo ($P \leq .001$), with placebo-induced improvement a median of 29% of the improvement in PC_{20} attributable to salmeterol. There was no significant difference between the methacholine PC_{20} after single-blind salmeterol (visit 3) and double-blind salmeterol (visit 4 or 5). Thus our study found an objectively measured placebo response in bronchial hyperresponsiveness that provided approximately one third the benefit of active drug (salmeterol) in the same individuals under identical conditions.

The second aim of this study was to define a placebo responder to identify determinants or predictors of placebo response. The study protocol allowed for examination of the normal variation in airway hyperresponsiveness to ensure that any placebo response fell outside that range. At

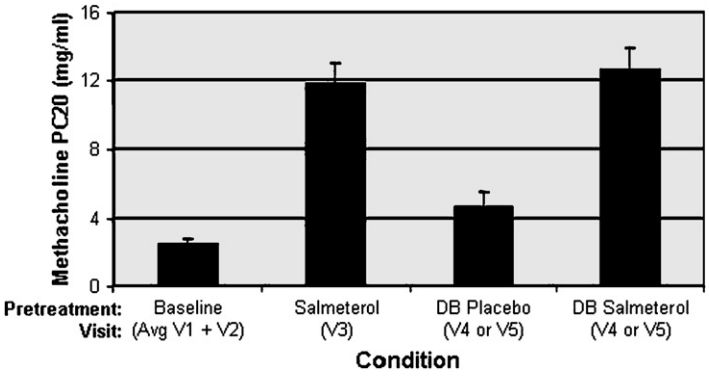

FIG 2. Bronchoprovocation response by visit. All subjects demonstrated bronchial hyperresponsiveness (PC_{20} $\leq$4 mg/mL) at baseline (average of visits 1 and 2), which was significantly reduced by pretreatment with (single-blind) salmeterol at visit 3. Visits 4 and 5 included pretreatment with (double-blind *[DB]*) placebo or salmeterol (in a randomized order) before methacholine challenge. Double-blind placebo induced a significant increase in methacholine PC_{20} ($P = .001$) compared with baseline values. *V*, Visit.

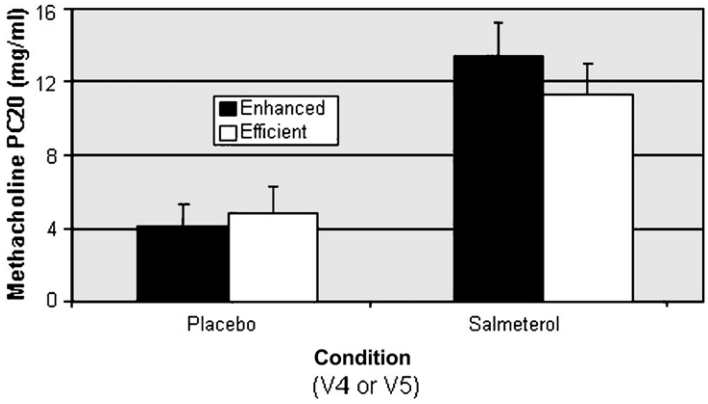

FIG 3. Bronchoprovocation response by physician interaction. Subjects were randomized to physician interaction style (enhanced or efficient for visits 4 and 5) and to premethacholine treatment order (placebo/salmeterol or salmeterol/placebo). No primary effect of physician interaction style was detected. *V*, Visit.

the first 2 screening visits, 74.5% of subjects had identical concentrations of methacholine, which induces a decrease in FEV_1 of at least 20% from the baseline value (methacholine PD_{20}), which is distinguished from the PC_{20}, an interpolated value, and the remaining 25.5% had a PD_{20} within 1 doubling dose of their initial value at the second screen; no subjects had a difference in PD_{20} of 2 or more dose levels. We concluded that a difference of 2 or more dose levels between the screening and placebo visits was unlikely because of random variation and *post facto* defined as placebo responders all subjects who met this criterion. Ten (18.2%) subjects showed a 2-dose difference between their last screening visit and their placebo visit (51% showed 1 dose level of improvement). This subsample had a large placebo/salmeterol PC_{20} ratio (median, 0.50; mean, 0.86). Unexpectedly, 5 (9%) subjects had a postplacebo PD_{20} of greater than 25 mg/mL (the highest concentration of methacholine used for this study).

Predictors of placebo response

Demographics and psychologic characteristics. Sex and BMI did not differ between placebo responders versus nonresponders, but responders were significantly younger than nonresponders (responders, 24.0; nonresponders, 30.9; $P \leq .01$). Responders did not differ from nonresponders in baseline psychologic characteristics, including positive or negative trait affect, depression, hostility, or trait optimism (all $P > .10$).

PC_{20} responses by physician condition (enhanced vs efficient). There was no significant difference in the number of placebo responders in the efficient versus the enhanced physician conditions ($P > .10$). In addition, there was no significant difference between enhanced and efficient conditions in PC_{20} levels at either the placebo or the salmeterol visit ($P > .1$, Fig 3) nor in the size of the placebo response (the difference between PC_{20} at the placebo and the mean screening visits [mean difference: enhanced, 2.06; efficient, 2.27; $P > .1$]). The ratio of placebo to salmeterol PC_{20} did not differ by condition ($P > .1$). There was not a significant main effect of physician condition for PC_{20} in the placebo condition controlling for values during the screening and single-blind salmeterol visits ($P > .1$) or in PC_{20} levels at the salmeterol visit ($P > .1$).

Psychologic responses by physician conditions. The subjects assigned to the 2 physician encounter groups differed in their ratings of the physicians, with those assigned to the enhanced group rating their physicians as significantly more supportive and optimistic than those assigned to the efficient group ($P < .05$), suggesting that the manipulation of physician behavior successfully altered perceptions in the desired direction. However, the 2 groups did not differ in their treatment outcome expectancies or in their levels of anxiety, positive or negative mood, or asthma-related cognitive disturbance during the waiting period (all $P > .1$), leading us to conclude that this altered perception did not affect potential mediators of the placebo response. Interestingly, across physician encounter conditions, placebo responders described their physicians as less optimistic during the encounter than nonresponders ($P < .05$), particularly those in the enhanced condition ($P < .05$). Responders and nonresponders did not differ in their treatment outcome expectancies or in the levels of anxiety, positive or negative mood, asthma-related cognitive disturbance, and other perceptions of the physician during the period between the physician encounter and the methacholine challenge (all $P > .1$).

DISCUSSION

The last decade has seen an increased interest in the placebo response in physical disease, and placebo effects have been documented in numerous conditions.[2] Recently, the neural circuitry underlying these effects has begun to be mapped.[20] However, the vast majority of studies examine effects in subjectively experienced outcomes, such as pain and depression, suggesting higher-order brain modulation of central processes relevant to these conditions. Relatively little is known about the ability of a placebo to alter objectively assessed peripheral end points directly relevant to disease. In this study we demonstrate that a placebo bronchodilator can significantly reduce nonspecific airway hyperresponsiveness in asthmatic subjects: postplacebo PC_{20} was almost twice that observed during the 2 screening visits. Thus although placebo medications are pharmacologically inert, they can be biologically active, modulating peripheral physiologic processes, presumably by activating specific neural circuits.

Using our within-subject design, we defined placebo responders *post facto* by comparing airway responses after administration of placebo bronchodilators with the subjects' own untreated baseline responses. We strictly defined a placebo response as a change greater than any that occurred between the 2 initial screening visits. Eighteen percent of subjects were characterized as placebo responders by using the strict criteria of a 2-dose or greater difference between screening and postplacebo PD_{20}. In this highly responsive group the median placebo/salmeterol PC_{20} ratio was 50% (compared with 29% overall). We almost certainly underestimated the number of placebo responders by using these criteria; 53% of subjects showed a 1-dose difference in PD_{20} between screening and placebo visits, some of whom were likely manifesting a placebo response (albeit to a lower degree). We also found a small group (n = 5 [9%]) who demonstrated a less than 20% FEV_1 decrease from the maximum methacholine concentration, suggesting that in selected individuals the placebo response can completely eliminate bronchial hyperreactivity. The potential clinical significance of this magnitude of placebo response, much higher than could be accounted for by natural history or random variation in responsivity, is substantial. These findings demonstrate an objectively measured and clinically relevant placebo effect in a cardinal manifestation of a highly prevalent and morbid disease.

The size of the placebo effect in a clinical trial is often calculated as the benefit in the placebo arm relative to the benefit in the active drug arm. In many studies the placebo effect is about one third of the active drug effect, despite all the sources of variation that contribute to this value, such as between-subject differences and random fluctuation.[21] Interestingly, we found that the median placebo PC_{20} over the active drug PC_{20} was 29%, even in the context in which between-subject effects were eliminated and the placebo effect was determined relative to the subjects' own baseline PC_{20} values. Thus placebo responses in this objective outcome might be meaningful clinically.

Although there was substantial variation in the magnitude of the placebo response, we were generally unsuccessful in predicting this variability. Many of the factors (traits such as optimism and negative affect) considered potential predictors of the placebo response were not predictive in this context. However, although placebo responders did not differ from nonresponders on the basis of sex or BMI, responders were significantly younger, a finding that merits further study.

We attempted to enhance the placebo response by physician encounters that promoted positive expectancies about the efficacy of the prechallenge treatments. Physicians in the enhanced encounters were intensively trained to convey positive expectancies, communicate authoritatively, and engage the research subject supportively. Subjects assigned to this condition rated their physicians as significantly more supportive and optimistic than those assigned to the neutral expectation condition, as was the goal, suggesting that the physician training was successful. However, manipulating the subjects' perceptions in this manner altered neither expectations regarding drug efficacy nor differences in airway responsivity. Future research directed at discovering methods for promoting the placebo response is clearly warranted. We might have had different results if the physician interactions were designed to promote enhanced versus negative (rather than neutral) expectancies; likewise, it is possible that the adverse symptomatic responses to the methacholine challenges were too mild to be substantially affected by the asthmatic subjects' anticipatory anxiety or expectations.

Self-reported expectations of symptoms before the methacholine challenge did not predict lung function in the placebo or active drug conditions. Other psychologic

responses to the encounter, such as mood state or asthma-specific cognitive disturbance, also did not predict placebo responses.

Interestingly, subjects' perceptions of physician optimism appeared to predict placebo response in a direction opposite to our hypothesis. We found that placebo responders described their physician as less optimistic overall. This was true in both groups but most strongly in the enhanced encounters, despite the physicians' training to convey optimism about drug efficacy and overall (responders plus nonresponders) perception of these physicians as more optimistic. Placebo responders in the enhanced condition viewed the physician as moderately to very optimistic, whereas nonresponders viewed them as very to extremely optimistic. The relationship between placebo response and optimistic attributions was not observed in subjects assigned to the efficient encounter, with more equivocal expectations. It is possible that placebo responders have a more accurate or realistic view of their physicians' actual drug efficacy expectations because physicians in the enhanced condition communicated a more optimistic expectation than they knew was realistic (because all subjects received placebo). This difference would not be seen in the efficient condition because those physicians transmitted an equivocal expectation more consistent with their actual view. This finding is consistent with the trend in the data suggesting that in the enhanced (but not efficient) condition placebo responders expected more symptoms with challenge than nonresponders. Future research might manipulate physician expectations to determine whether these ''real'' expectations affect patient placebo responses.

Another possible interpretation of these findings is that the positive expectation message in the enhanced condition was muted by the physicians' enhanced emotional care/supportiveness behavior (eg, by discussing concerns more and asking more questions), which could have inadvertently conveyed that they were not actually optimistic about the subjects' outcome. With this design, it was impossible to untangle the effects of the expectancy part of the manipulation from the supportive care component.

A great deal is now known about the specific brain circuits that mediate cognitive control and mood regulation.[22-24] Placebo effects on brain activity have been demonstrated in pain, depression, and Parkinson disease.[20,25-29] Placebo response appears to involve both cortical regions of the brain involved in cognition and the subcortical regions that process emotions (including the ventral striatum). Tight linkages have been demonstrated between cortical areas activated by executive functions or affective states and the deep structures of the brain associated with peripheral physiologic monitoring and control. We hypothesize that a placebo response can be mediated through modulation of neural efferent pathways (inhibition of cholinergic[30] or activation of nonadrenergic-noncholinerigic parasympathetic[31-34] outflow) or even through regulation of central nervous system active inflammatory mediators, such as TNF-α or arachidonic acid metabolites.[35] Because cholinergic blockade might have a greater effect on larger airways,[36] nonadrenergic noncholinergic innervation responses or modulation of inflammatory mediators might be a more likely mechanism for our findings. Our current findings suggesting placebo control of lung function support the conclusion that the central nervous system correlates of higher mental function not only affect responses within the brain itself but might also produce peripheral changes in ways that can affect health.

We have documented a placebo response in objective, health-relevant measures of lung function; this contradicts recent suggestions in the literature that placebo responses are confined to subjective outcomes, such as pain. Defining the links between psychologic processes, their neural substrates, and peripheral physiology is a critically important area of medicine. According to the Institute of Medicine, ''since approximately half of all causes of morbidity and mortality in the United States are linked to behavioral and social factors it is crucial to improve our understanding of these issues.''[37] Understanding the nature of the placebo response in disease is one reasonable approach to addressing these issues.

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APPENDIX.

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